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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	
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03/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,976	SCHELLER ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,14,16-18,20 and 24-52* is/are pending in the application.

4a) Of the above claim(s) *37-39, 50-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,14,16-18,20,24-36,40-49 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/13/08 and 12/04/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of the species SPM-927, drawn to a compound of the formula IIb wherein Ar is unsubstituted phenyl, R3 is methoxymethyl, R1 is methyl and CSD associated condition is "chronic headache" in the reply filed on December 4, 2009 is acknowledged. The traversal is on the grounds that the genera of formula IIb and CSD associated conditions are not so large as to impose undue search burden.

2. Applicant's arguments have been carefully considered and deemed persuasive with regards to the compositions. However, with regards to the associated conditions, Examiner maintains the election of species requirement for the reasons of record, namely that the diseases have, e.g., different etiologies, symptoms, and population, therefore searching all CSD associated conditions would be burdensome. A reference which would anticipate/make obvious one of the treatments would not necessarily anticipate/make obvious another treatment.

Therefore the election of species requirement with respect to the CSD associated conditions is maintained and the election of species requirement with respect to the compounds within the methods of prevention/treatment is herein withdrawn.

Status of the claims

3. Claims 1-4, 14, 16-18, 20, 24-52 are pending in the application. Claims 37-39 and 50-51 are withdrawn. Claims 1-4, 14, 16-18, 20, 24-36, 40-49 and 52 are readable upon the elected species/group and are therefore presented for examination on the

merits. Please note that claim 40 was previously added to Group II, but it should have been in Group I, so it is now being examined.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 1-4, 14, 16-18, 20, 24, 32-36, 41, 44, 46-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris (US 2002/0086828) and under 35 U.S.C. 102(e) as being anticipated by Harris (US 6,884,910, cited in the IDS dated 12/4/2009).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris discloses a method of treating chronic headaches, migraines and acute migraines with the compound (R)-2-acetamido-N-benzyl-3-methoxypropionamide and also with other compounds embraced by the genus of Formula II, i.e., O-methyl-N-acetyl-D-serine-p-fluorobenzylamide, O-methyl-N-acetyl-D-serine-p-fluorobenzyl amide, etc. (e.g., pages 7-8).

Harris teaches that a migraine headache is defined as a periodically occurring (i.e., chronic) vascular headache characterized by pain in the head (usually unilateral), nausea and vomiting, photophobia, phenophobia, vertigo and general weakness. Migraine is the most common type of vascular headache and affects as amny as 15% of the world's population. Of the different types of migraines, classical migraine and common migraine are the two most prevalent. The major difference between the two types of migraines is that classical migraines are preceded by the appearance of neurological symptoms before an attack whereas common migraines are not preceded by such symptoms. Migraine is caused by intermittent brain dysfunction. However, the precise pathophysiological mechanism involved are not understood. The head-pain is believed to involve blood vessel dilation and a reduction of the brain's pain relieving chemicals. Harris teaches that analgesics are often used to treat infrequent and mild migraines. Analgesics reduce the pain of a migraine in the case of aspirin also discourage clumping of blood platelets. However, for moderate to severe migraines, stronger medication is necessary, e.g., ergotamine, or 5-H-T1 agonists like sumatriptan (page 1). Harris goes on to teach that alternatives for treatment are necessary given the inadequacy of current therapy in completely alleviating the pain from those who

have moderate to heavy (i.e., acute) migraine headaches (page 1).Harris discloses that a migraine headache is a paroxysmal disorder characterized by recurrent attacks of headaches, which may be associated with visual (as in cluster type headaches) or GI disturbances, the pain is usually generalized, but it may also be a unilateral throbbing (as in cluster type headaches), which begins around one of the eyes and then spreads through the head to involve one or both sides. In severe cases, it is accompanied by anorexia, nausea and vomiting and photophobia. In addition, the extremities are cold and cyanosed, and the patient is irritable. Moreover, the scalp arteries are prominent and their amplitude of pulsation is increased. The compounds of Harris are useful in the prophylaxis and the treatment of migraine headaches and alleviating the pain associated therewith. They are administered to patients with migraine headaches in pain relieving amounts. The discussions associated with therapeutic effective amounts are applicable to the treatment and/or prophylaxis of migraine headaches (e.g., page 13).

Harris teaches that resulting mixtures of isomers can be separated into the pure isomers by methods known to one skilled in the art, e.g., by fractional distillation, crystallization and/or chromatography (see, e.g., page 11). With regards to dosages, in a preferred embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic

situation. The compounds of Harris may be administered orally as tablets, troches, capsules, etc. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention contains between about 10 mg and 6 g of active compound. (e.g., page 13). The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form. A unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/mL of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients. The term patient or subject refers to a warm blooded animal, preferably mammals, such as cats, dogs, cows, pigs, mice, rats and primates, including humans. The Harris reference teaches all the active steps and population as required by claim 1, therefore, with regards to the limitation “treating a condition associated with cortical spreading depression CSD in a subject” it is deemed that it would be inherent to the method of treating headaches, migraines, chronic headaches, etc. with compounds such as (R)-2-acetamido-N-benzyl-3-methoxypropionamide as taught by Harris (See MPEP 2112). With respect to the term “prevention" please note that it does not require that the subject be afflicted with the disease. Thus, administration to a subject (e.g., Examples 1-7, pages 15-18) reads

upon prevention of a condition associated with cortical spreading depression (CSD) in a subject including the conditions of instant claims 41 and 46.

Therefore the reference is deemed to anticipate the instant claims thereof.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 26-31, 42-45, 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris (US 2002/0086828) and over Harris (US 6,884,910, cited in the IDS dated 12/4/2009).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris is relied upon as above. Further, Harris teaches that the physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, and the type of malady being treated. He or she will generally wish to initiate treatment at small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached (e.g., page 12). With regards to dosages, in a preferred embodiment, the

compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. The compounds of Harris may be administered orally as tablets, troches, capsules, etc. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention contains between about 10 mg and 6 g of active compound. (e.g., page 13). The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form. A unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/mL of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

Harris does not expressly teach frequencies instantly taught (e.g., daily, weekly, three doses per day, increasing doses, etc.).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine such frequencies and mode of administration based on the teachings of Harris. One of ordinary skill in the art at the time the invention was

made would have been motivated to do so because Harris teaches that the physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, and the type of malady being treated. He or she will generally wish to initiate treatment at small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because such adjustments were known to be within the purview of those of ordinary skill in the art.

Furthermore, with regards to the dosages, Harris does not expressly teach an absolute daily dosage. However, Harris does provide guidance in the form of therapeutic amount in an unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Also, in a preferred embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. For a human weighing, e.g., 100 kg, thus the daily dosage would be from 100 mg/day to 10 g/day. The dosage as taught by Harris depends on weight and all the claimed ranges are obtainable by changing the weights of the subjects. One of ordinary skill in the art at the time the invention was made would have been motivated to determine the appropriate amounts per day based on the dosage parameters taught by Harris. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of

success because such adjustments were known to be within the purview of those of ordinary skill in the art.

With regards to the limitation drawn to plasma concentration, please note that the Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether Applicants' plasma concentration (within the claimed method) differs and, if so, to what extent, from that of the discussed reference. Therefore, with the showing of the reference, the burden of establishing non-obviousness by objective evidence is shifted to the Applicants. Further, with respect to the dosages and concentrations instantly claimed: "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (MPEP 2144.05).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Claims 40, 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris (US 2002/0086828) and over Harris (US 6,884,910, cited in the IDS dated 12/4/2009).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris is relied upon as above. Harris teaches that analgesics are often used to treat infrequent and mild migraines. Analgesics reduce the pain of a migraine in the case of aspirin also discourage clumping of blood platelets. However, for moderate to severe migraines, stronger medication is necessary, e.g., ergotamine, or 5-H-T1 agonists like sumatriptan (page 1). Harris also teaches that in the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use more than one active ingredient for the treatment of migraines or chronic headaches such as sumatriptan. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." (MPEP 2144.06). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since Harris Harris also teaches that in the case of compositions containing

supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

. Further, with respect to the dosages and concentrations instantly claimed: "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (MPEP 2144.05).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

9. No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 02/2010